REMARKS

Claims 32-33, 38, 41-47, 49 constitute the pending claims in the present application. New claims 50-63 have been added. Support for the matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

Applicants submit that there are a substantial number of examples in current clinical trials and in the literature citing attempts to use pharmaceutical preparations, including cell and tissue grafts, in the treatment of neurological diseases. Therefore, one of skill in the art would be enabled to use the claimed subject matter, in light of the prevailing evidence in the field. Examples of this work can be found both prior to and since the filing of the present application (Galpern et al. (1996) ; Kordower et al. (1996); Uchida and Toya (1996); Shetty and Turner (1996); Mahoney and Saltzman (1996); included herewith as Exhibits 1-5).

Applicants respectfully remind the Examiner that the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. Dickinson v. Zurko, 119 S.Ct. 1816 (1999). In light of the Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant

art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. Applicants respectfully request reconsideration and withdrawal of this rejection.

2. Claims 32, 43-45, and 49 are rejected under U.S.C. 102(a) for allegedly being anticipated by Sosnowski et al. Applicants maintain that the claims, as written, disclose matter patentably distinguishable from and not anticipated by that taught by Sosnowski et al. However, to expedite prosecution, Applicants amend claim 49 and add new claims 50-63 to more explicity describe the cellular properties of the invention. Applicants note that these amendments are not made in acquiescence of the rejection.

Applicants' cells are different from those taught by Sosnowski et al. based on several criteria. One striking difference, outlined extensively in the specification and now included by amendment to the claims, is the non-adherent characteristics of the Applicants' cells (for examples see Figure 1 and page 14, lines 4-5 of the specification). Applicants characterize the behavior of the cells in culture as forming "floating spheres which are named olfballs." (page 14, lines 4-5). This characteristic serves not only as a useful means of purifying the cells from non-stem cells, but also denotes the physical properties of these cells. The cells taught by Sosnowski et al. are characterized as round, which denotes their shape and distinguishes them from other cells in the cultures such as polygonal cells. However, a round shape does not imply that the cells are non-adherent, and there is no indication that the cells of Sosnowski et al. possess any such specialized phenotype.

This non-adherent phenotype of the Applicants' cells has other implications for the distinctness of the cells of the instant invention over the cells taught by Sosnowski et al. One of skill in the art will readily appreciate that the adherent properties of a cell or cells has implications for the expression of extracellular matrix, cell surface, and cell adhesion proteins (for review see Gilbert, Developmental Biology, 4th edition, chapter 3). Gilbert reviews an extensive body of work beginning in the late 1930's that recognized that various cell types have different adhesion properties, that these properties are critical for the behavior of cells, and most recently that these adhesion properties are the result of differential expression of various cell

adhesion molecules (CAMs) that mediate interactions both among cells and between cells and the extracellular matrix. Therefore, the non-adherent clusters (Olf-Balls) of the invention possess a range of cellular and molecular differences apparent to one of skill in the art that readily distinguish these cells from those taught by Sosnowski et al.

The cells of the instant invention differ from those taught by Sosnowski et al. in another critical way. Claim 49, and new claims 50-63 specify that Applicants' cells are "stem cells". This is an important term that, although often used somewhat loosely and incorrectly, implies several properties. These properties are specifically defined by Applicants in the specification, and include both the ability to proliferate to generate daughter cells and the ability to renew by producing more stem cells (page 4, lines 8-14). Applicants' cells meet these criteria (page 8, lines 5-8). In contrast, the cells taught by Sosnowski et al. do not meet the widely accepted definition of stem cells outlined in the specification. The cells of Sosnowski et al. are perhaps progenitors, but they fail to display the property of self-renewal that is a key distinguishing feature of true stem cells. The progenitor cells of Sosnowski et al. (described as round cells in the text) decreased in number after 4-8 days in culture (page 45, column 1).

Amended claim 49 and new claims 50-63 clearly delineate the properties of the cells of the instant invention that make them patentably distinct from the cells taught by Sosnowski et al. Applicants' invention teaches cells which meet the criteria of stem cells accepted by those of skill in the art including the capacity to self-renew, whereas the cells taught by Sosnowski et al. fail to possess this property. Additionally, Applicants' invention possesses adhesive properties distinguishable from Sosnowski et al. that allow Applicants' cells to grow as "non-adherent clusters". Such differences in adhesive properties have implications for protein expression apparent to one of skill in the art. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

3. Claim 38 is rejected under 35 U.S.C. 102(a) as being anticipated by Sosnowski et al. in light of Fraichard et al. Applicants maintain that the claim, as written, is distinguishable from the cells taught by Sosnowski et al. However to expedite prosecution, Applicants have amended

claim 38 to more explicitly describe the non-adherent properties of the claimed cells, as described in detail in the specification. Applicants note that the amendment is not made in acquiescence of the rejection.

The claimed cells are isolated and cultured based on their non-adherent properties, as outlined in the specification (for examples see Figure 1 and page 14, lines 4-5). This is an important distinction from the cells taught by Sosnowski et al. for the reasons discussed in detail above. Thus, these cells are certainly different cells with different physical properties. These differences between the two cell types are separable from and exist independently of whether the cells taught by Sosnowski et al. also inherently express nestin, as asserted in the prior Office Action. The existence of a population of cells with such substantially different physical properties was in no way taught or even referred to by Sosnowski et al.

Additionally, Applicants disagree with the assertions of Fraichard et al., as cited in the prior Office Action, that it is an "inherent property of neuroepithelial stem cells to express nestin," and therefore the cells taught by Sosnowski et al. are also nestin positive. Pixley studied rat olfactory progenitor cells using a dissociated cell culture system, and found that "[a]ntibodies to nestin did not label olfactory neurons or progenitor cells." (Pixley, 1996, International Journal of Developmental Neuroscience, abstract, enclosed as Exhibit 1). Therefore, it is not an inherent property of neuroepithelial progenitor cells to express nestin, and absent any direct evidence presented in Sosnowski et al., expression of nestin is a distinct and non-anticipated characteristic of the Applicants' invention over that taught by Sosnowski et al.

Amended claim 38 teaches a culture of cells specified by their adherence properties and by expression of a marker, nestin. Applicants maintain that both of these criteria are distinct and non-anticipated by the cells of Sosnowski et al. Applicants respectfully request reconsideration and withdrawal of this rejection.

4. Claim 33 is rejected under U.S.C. 103(a) as being unpatentable over Mayo et al. in view of Kaufman et al. Applicants traverse this rejection. Mayo et al. teaches an analysis of cells

which can contribute to the tongue, and defines these cells with respect to the expression of the marker desmin. Kaufman et al. had previously established that the expression of desmin is a characteristic of replicating myoblasts. Although claim 33 teaches the isolation of stem cells from the tongue, these cells are distinct from the cells taught by Mayo et al. even in light of Kaufman et al.

The cells of both of these references are muscle precursor cells. This is underscored by Mayo et al. in which the cells in question actually originate in the somites, and migrate to contribute to the **musculature** of the tongue. In contrast, the cells of claim 33 are produced by culturing tissues containing sensory receptors. The tongue, as used by Applicants, is a source of sensory receptors, not muscle progenitors. These distinct populations of cells within the tongue differ in both their gene expression profiles, and in their differentiative capacity. For example, the cells of claim 33 express nestin, while the cells of Mayo et al. and Kaufman et al. express desmin. Additionally, the cells of claim 33 differentiate to produce neurons and neuronal support cells, while the cells in the cited references contribute to the myogenic lineage. No evidence is presented in these references to suggest that the myogenic progenitor cells of the tongue are capable of contributing to neuronal cells.

Finally, Applicants' point out that the amendments made to claim 49, upon which claim 33 is dependent, specify the adhesive properties of the cells of the instant invention. The ability of these cells to form non-adherent clusters in culture further distinguishes the population of cells isolated from the tongue in the invention from the cells taught by Kaufman et al. and Mayo et al.

Applicants' submit that complex three dimensional tissues and organs like the tongue are comprised of many cell types of distinct lineage. Therefore, the isolation of two cells from a specific tissue does not imply that the two cells possess the same, or even similar properties. The cells of the instant invention are obtained from tissue containing sensory receptors, and can differentiate to produce neuronal cells. The cells of Mayo et al., although capable of contributing to the tongue, contribute to the musculature of the tongue not to the sensory receptors of the tongue. A common point of origin does not impart two cells with the same properties or function. Taken to its logical extreme, such an analogy would mean that every cell in an

organism is patentably indistinct because each arises from a single cell, the fertilized egg. Applicants respectfully request reconsideration and withdrawal of this rejection.

5. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as unpatentable over Sosnowski et al. in view of LaSalle et al. Applicants respectfully traverse this rejection.

Claims 41 and 42 deal with the expression of a heterologous gene in the stem cells of the invention. Applicants' method for transfecting the stem cells are detailed in the specification (Example 8, pages 23-24; Example 10, page 26). The Examiner correctly points out that the claimed invention involves use of an adenoviral vector to express β-galactosidase. However, this is distinct from the method taught by LaSalle et al. Although LaSalle et al. teaches the infection of cells with an adenoviral vector expressing β-galactosidase, LaSalle et al. infected "quiescent nerve cells", not progenitor or stem cells. This work provided no experimental evidence that adenoviral mediated transfection would be possible in progenitor or stem cell populations. The experimental evidence presented by Applicants in the specification was essential to demonstrate that such transfection was possible, and that adenoviral mediated transfection does not affect the growth properties of the stem cells. None of these points were addressed by LaSalle et al., and the skilled artisan would have no way of determining, *a priori*, the results of experiments regarding the adenoviral mediated transfection of stem cells based only on knowledge that such a procedure was possible for quiescent cells.

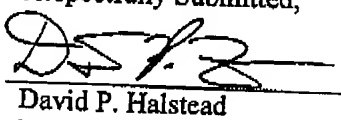
Applicants' note that the amendments to claim 49 and the addition of claims 50-53 distinguish the cells of this invention from those taught by Sosnowski et al., as discussed in detail above. However, even in light of Sosnowski et al., which teaches the isolation of a progenitor population of cells, it is still a large step from the knowledge of a progenitor population of cells to the successful manipulation of such cells. Specifically, the vastly different growth and protein expression properties of the cells of the instant invention from those taught by Sosnowski et al., including specialized adhesive characteristics, makes it impossible to draw experimental conclusions from the experiments conducted in LaSalle et al., even in light of Sosnowski et al.

Claims 41 and 42 disclose the transfection of the claimed cells with a heterologus gene. In light of the teachings of LaSalle et al. and the isolation of a type of progenitor cell by Sosnowski et al., the transfection of stem cells with heterologous genes may have been obvious to try. However, obvious to try is distinct from obvious, and the skilled artisan will recognize that one could not have predicted the outcome of adenoviral mediated transfection of stem cells based on the transfection of quiescent cells. Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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